REMARKS

Claims 1, 3, 6 and 11 are pending in this application. Claims 1, 3, and 6 have been withdrawn from consideration. Claim 11 has been rejected. Claims 1, 3, 6 and 11 have been canceled. Claim 21 has been added. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Election/Restriction Requirement

The Examiner acknowledges the Election of Group II in the reply received 10/15/07. While the Examiner suggests that the election was made without traverse, Applicants respectfully point out that the last paragraph of the reply states that the election of Group II was made with traverse. Correction of the record to reflect the traverse is, therefore, requested.

II. Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claim 11 has been rejected under 35 U.S.C. 112, second paragraph as being indefinite. Specifically, it is suggested that step (b) of claim 11 requires detecting "one or more polymorphisms" in a thymidylate synthase (TS) nucleic acid molecule that was obtained from an individual; however, it is suggested that it is not clear how one detects a polymorphism in an individual. It is further suggested that it is unclear how the three portions of the wherein clause refers to different positions or combinations of positions within the TS nucleic acid thereby creating a disconnect between the process steps which require the detection of one or more unspecified polymorphisms and the "wherein" clauses which refer to alleles at particular

polymorphic positions. Applicants respectfully disagree with this rejection. However, in the interest of facilitating the prosecution of this application, Applicants have canceled claim 11 and added new claim 21 which clarifies the detection of specific polymorphisms in a thymidylate synthase nucleic acid molecule from a subject. Support for new claim 21 is found in claim 11 as originally filed and in paragraphs [0035]-[0044] and [0050] of the specification.

III. Priority

Priority to U.S. Serial No. 60/420,164 has not been granted because it is suggested that the disclosure of the prior-filed application fails to provide adequate support or enablement for the +6/-6 deletion polymorphism referred to in claim 11. Applicants respectfully disagree. In particular, it is respectfully submitted that, as currently amended, the subject matter of claim 21 is fully supported and enabled by the '164 application. As such reconsideration of priority to the '164 application is respectfully requested.

IV. Claim Rejections Under 35 U.S.C. §102

Claim 11 has been rejected under 35 U.S.C. 102(a) and 102(b) as being anticipated by Ulrich et al. ((June 2002) *Cancer Res.* 62:3361-3364). It is suggested that this reference teaches a method comprising obtaining a nucleic acid sample comprising a TS nucleic acid molecule and detecting the alleles for one or more polymorphisms. It is suggested that Ulrich et al. detect the alleles present in the 28-bp repeat polymorphism and the 3'UTR 6-bp deletion polymorphism, and further teach that the 3R/3R

genotype is associated with an increased risk of developing cancer in patients with low or medium folate intake. The Examiner suggests that Ulrich et al. teach that the 6-bp repeat is not associated with risk of colorectal cancer and therefore, the association with the 3R/3R genotype would be present with the + or - 6-bp alleles.

Applicants respectfully traverse this rejection. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

In the instant case, Applicants have found that the 3R/3R, 3R/3RV, 2R/2R, 2R/3R, 2R/3RV constructs and the -6 bp/1494 deletion polymorphism can be used to determine the likelihood of TS disruption and thus the presence of cancer. See paragraph [0050] and Table 1 at page 28. In contrast, Urlich et al. disclose a gene-nutrient interaction between the 3R/3R and folate intake, with no correlation between the 3R/3R construct and the +6 bp/1494 3' untranslated region polymorphism with colorectal cancer. Accordingly, this reference cannot be held to anticipate the invention as currently presented. It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

Claim 11 has been further rejected under 35 U.S.C. 102(a) as being anticipated by Mandola et al. ((2003) *Cancer Res.* 63:2898-2904). It is suggested that this reference teaches detecting alleles present in the common repeat polymorphism of the 5' UTR of the TS gene and also of a single nucleotide polymorphism

within this gene. It is further suggested that Mandola et al. teach that an additional 28 bp repeat within the 5′ UTR can enhance transcriptional activation of TS due to the presence of a USF binding site in the repeat, wherein a SNP can abolish the ability of USF proteins to bind to this site. It is acknowledged that Mandola et al. are silent to the relationship of these polymorphisms to predisposition to cancer or CVD, however the claimed method steps are carried out and the relationships to particular diseases are inherent properties.

Applicants respectfully traverse this rejection. In particular, it is respectfully submitted that Mandola et al. provide no teaching or suggestion of the +6 bp/1494 3' untranslated region polymorphism and its association with colorectal cancer. Because the claim as currently presented specifies the detection of both the 3R/3R construct and +6 bp/1494 3' untranslated region polymorphism, Mandola et al. cannot be held to anticipate the present invention. It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

Claim 11 has been further rejected under 35 U.S.C. 102(a) as being anticipated by Kawakami et al. ((Sept. 2003) *Cancer Res.* 63(18):6004-7). It is suggested that this reference teaches the detection of alleles present in the common repeat polymorphism of the 5′ UTR of the TS gene and also of a SNP within this gene. It is suggested that Kawakami et al. teach that an additional 28 bp repeat within the 5′ UTR can enhance transcriptional activation of TS due to the presence of a USF binding site in the repeat, wherein a SNP can abolish the ability of USF proteins to bind to this site. It is acknowledged that Kawakami et al. are silent to

the relationship of these polymorphisms to predisposition to cancer or CVD, however the claimed method steps are carried out and the relationships to particular diseases are inherent properties.

Applicants respectfully traverse this rejection. In particular, it is respectfully submitted that Kawakami et al. provide no teaching or suggestion of the +6 bp/1494 3' untranslated region polymorphism and its association with colorectal cancer. Because the claim as currently presented specifies the detection of both the 3R/3R construct and +6 bp/1494 3' untranslated region polymorphism, Kawakami et al. cannot be held to anticipate the present invention. It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

Claim 11 has been further rejected under 35 U.S.C. 102(b) as being anticipated by Lenz et al. ((March 2002) *Proc. Am. Assoc. Cancer Res.* 43:Abstract 3274). It is suggested that this reference teaches a method which comprises obtaining a nucleic acid sample comprising a TS nucleic acid molecule and determining the allele present at the site of the 6-bp deletion polymorphism in the 3'UTR of the TS gene. The Examiner suggests that Lenz et al. teach that patients possessing one or two deletion alleles showed a relative risk of 1.4 when compared with patients having no deletion allele.

Applicants respectfully traverse this rejection. Lenz et al. disclose "a novel 6-bp deletion in the 3 UTR of the TS gene" with no teaching or suggestion that the deletion is located at position 1494 of the TS mRNA. Moreover, this document provides no teaching or suggestion of detecting both the 3R/3R construct and

+6 bp/1494 3' untranslated region polymorphism and their association with colorectal cancer. Because the claim as currently presented specifies the detection of both the 3R/3R construct and +6 bp/1494 3' untranslated region polymorphism, Lenz et al. cannot be held to anticipate the present invention. It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

V. Claim Rejections Under 35 U.S.C. §112, First Paragraph

Claim 11 has been rejected under 35 U.S.C., first paragraph, for failing to meet the enablement requirement. It is suggested that the scope of the claim as it relates to polymorphisms and the two recited classes of diseases is quite broad and the specification does not provide a single experiment wherein alleles of the polymorphisms analyzed relative to populations of individuals with cancer or cardiovascular disease. It is alleged that the conclusions set forth in the claims are not based on empirical association studies between genotypes and risk or incidence of any type of cancer or cardiovascular disease. It is suggested that the claims are based on the potential effects of the polymorphisms on total folate load and the potential effects of folate load on disease risk. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the claim as currently presented is enabled by the teachings of the specification. Specifically, Table 1 at page 28, which provides the distribution of the 5'-TS tandem repeat polymorphism and the G->C polymorphism in the second repeat of the 3R among 99 non-hispanic white individuals with colorectal cancer. This data shows that 3R

allele is more frequently present in individuals with colorectal cancer. Moreover, paragraph [0106] and Table 3 provide the distribution of the +6bp/1494 polymorphism in 43 Caucasian individuals with colorectal cancer and the correlation of the same with TS expression. As such, Applicants have provided sufficient disclosure which demonstrates a correlation between the 3R/3R construct and +6 bp/1494 3' untranslated region polymorphism with colorectal cancer that one of skill in the art could make and use the present invention without undue experimentation. It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

VI. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **May 13, 2008**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515